



## Live-attenuated Respiratory Syncytial Virus Vaccines: Time for the Next Step

Dr. Karron and colleagues have previously made several attempts to develop a live-attenuated vaccine against respiratory syncytial virus (RSV) to protect children against one of the most common severe diseases during childhood (1). They have performed as many as seven phase I trials with different intranasal vaccine candidates. In this issue of the *Journal*, the study by Karron and colleagues (pp. 594–603) describes a pooled analysis of these early stage trials among 241 children aged 6–24 months (1). The authors took advantage of the postvaccination surveillance of acute respiratory infection used to monitor the occurrence of enhanced RSV disease in vaccine recipients to assess the overall vaccine efficacy and key immunogenicity endpoints. While analyzing these trials, they distinguished these vaccines into more and less immunogenic vaccines based on induced serum-neutralizing antibodies. Four vaccines that induced at least a fourfold increase in neutralization in  $\geq 80\%$  of the vaccine recipients were referred to as “more promising” vaccines, in opposition to “less promising” ones. Pooling data from trials with these more immunogenic vaccines, vaccine efficacy against RSV-associated medically attended respiratory infection was 67%, which suggests these vaccines might indeed hold a promise for RSV-naïve children.

How does this study fall within the current landscape of RSV immunization? The field is moving rapidly with products moving forward rapidly in clinical development. The front runner appears to be nirsevimab (previously MEDI8897), an extended half-life antibody targeting the prefusion RSV F protein, showing excellent safety and efficacy data in a recent trial in prematurely born children (2). This antibody has now moved into a phase 3 trial in healthy term children. A nanoparticle-based RSV F vaccine showed excellent safety and good but mixed efficacy after administration to pregnant women during their third trimester (3). The vaccine missed its primary endpoint by a fraction. Although efficacy in the United States could not be demonstrated, it showed impressive efficacy against most severe RSV infection in South Africa, leaving us with an ethical dilemma that this vaccine might have life-saving potential in developing countries. A chimpanzee adenovector-based vaccine nicely increased serum-neutralizing activity in older adults against some modest local adverse reactions (4). Finally, there are two late-stage trials investigating a prefusion RSV F subunit vaccine in pregnant women (5).

Most live-attenuated vaccines are administered intranasally and have been attenuated by deleting one or more genes,

including M2-2, NS2, SH, and G (6, 7). Intranasal live-attenuated RSV vaccines may have advantages over other approaches to prevent severe RSV infection. First, these vaccines are considered safe in general. Vaccine-enhanced disease, such as that encountered using formalin-inactivated RSV, has not been described with any live-attenuated RSV vaccine. In the case of insufficient attenuation, the vaccine may cause some respiratory symptoms, such as those observed with live-attenuated influenza vaccines (8). Second, needle-free vaccination has a clear advantage for preschool children. Third, the virus replicates in the airway, resulting in a broad immune response, including both a variety of specific antibodies as well as T-cell immunity, which may not be elicited by any other vaccine. Fourth, and this may be quite important for public health impact, live-attenuated RSV vaccines may induce herd immunity when administered to seronegative 6- to 24-month-old children (9).

The time seems right for live-attenuated RSV vaccines. Some of the candidate vaccines are the interesting and fruitful coproduction of a public–private partnership between the NIH and Sanofi pharmaceuticals (5). If live-attenuated RSV vaccines are indeed safe and effective, it is time that more candidate vaccines move forward in clinical development. There are nine active early stage trials with live-attenuated RSV vaccines, with only one in phase 2 registered on ClinicalTrials.gov. Has the bar so far been set too high to progress further into clinical development? Based on the paper by Karron and colleagues, we can conclude that the safety and efficacy profile of the group of live-attenuated RSV vaccines as well as their unique benefits over other approaches deserve a strong place in the turbulent future of RSV vaccine development. ■

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## Experimental Model for Studies of Pneumococcal Colonization in Older Adults

Pneumococci are major contributors to morbidity and mortality globally, being a major cause of community-acquired pneumonia, with or without septicemia, and bacterial meningitis, especially after the introduction of the Hib vaccine globally (1). The ecological niche for pneumococci is regarded to be the nasopharynx of young and healthy children and has been shown to carry pneumococci in the upper respiratory tract in up to 60% of cases (2, 3).

Pneumococcal colonization is believed to be a prerequisite for acquiring severe invasive pneumococcal diseases (IPD) (4). Young children and the elderly belong to the risk groups for getting IPD; hence, pneumococcal conjugated vaccines (PCVs) were introduced into childhood vaccination programs in many countries, leading to a dramatic decrease of IPD in vaccinated children (5–8). However, some studies have shown that nasopharyngeal colonization rates in children have remained the same after PCV introduction because of an increase of nonvaccine types, that is, serotype replacement with nonvaccine strains (7, 9).

Several studies show that nasopharyngeal colonization decreases with age and that it is lower in adults than in children (10). Also, it has been suggested that adults might be less susceptible to pneumococcal colonization. More knowledge is needed on why age influences colonization, which immune responses are evoked by pneumococcal colonization, especially in the elderly population, and to what extent a prior colonization might protect against recolonization. These issues are being addressed in this issue of the *Journal* in the study by Adler and colleagues (pp. 604–613) (11). Previous experimental model systems in humans with pneumococcal challenge have studied immune responses in younger adults (12), but here, Adler and colleagues are the first to challenge healthy older adults from 50 to 84 years of age, thus also including the risk group of the elderly above 65 years of age. In total, 64 adults were challenged with a pneumococcal strain of serotype 6B, originally isolated from the

nasopharynx of a child (13). The authors determined colonization rates by culture of nasal washes and humoral immune responses by anticapsular and antiprotein IgG levels. They found that colonization could be successfully established in 39% of the adults, though higher in the age group of 50 to 59 years (47%) than in those greater than or equal to 70 years of age (21%), suggesting that this model can be used for studies of pneumococcal colonization in all age groups. The authors conclude that colonization rates are similar between younger and older adults, but a larger study might be needed to clarify this issue, especially because only 14 participants were included in the 70- to 80-year-old group. In addition, only one pneumococcal strain was used in the study, and we know that there might be differences between strains of different serotypes in, for example, the ability to colonize, the length of carriage, and the pathogenicity. Moreover, pneumococci interact with other microbes in the respiratory microbiota, both other bacteria and viruses, which might affect colonization rates, and it has been shown that heterogeneity in the nasopharyngeal microbiome promotes pneumococcal colonization (14). One can speculate that the elderly might have more frequently undergone antibiotic treatment and that this could have reduced the diversity of the bacterial microbiome of the upper respiratory tract, as has been suggested previously (15). The expression of specific receptors of the nasopharyngeal epithelium that recognize pneumococcal proteins important for bacterial adhesion may also differ between individuals and influence colonization rates. Previously it has been described that aging and chronic inflammation were associated with enhanced expression levels in the lungs of receptors such as the pIgR (polymeric immunoglobulin receptor) (16). pIgR has been shown to interact with pneumococcal proteins such as PspC (CbpA), and hence this increased interaction might promote pneumococcal adhesion to epithelial and endothelial cells and disease development (17, 18). The current study opens possibilities to address these questions in a larger human experimental study including more participants, other pneumococcal serotypes, and data on the microbial nasopharyngeal flora and individual immune responses.

Interestingly, they observed that prior vaccination with 23-valent pneumococcal polysaccharide vaccine (PPV23) did not affect colonization rates in older adults. There are few data on the effect of

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